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Aging: A Sirtuin Shake-Up?

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The yeast sirtuin (Sir2) is a histone deacetylase that modulates yeast replicative life span by suppressing genome instability through chromatin modification. In this issue, Oberdoerffer et al. (2008) report that SIRT1, the mammalian ortholog of Sir2, is involved in DNA damage-induced chromatin reorganization, which promotes genome stability in mammalian cells.

First identified in yeast, silent information regulator 2 (Sir2) proteins, or sirtuins, are protein deacetylases or mono-ADP-ribosyltransferases present in organisms ranging from bacteria to humans. They target a wide range of cellular proteins in the nucleus, cytoplasm, and mitochondria and play a role in an ever-widening series of important biological processes, such as insulin secretion, fat mobilization, response to stress, and, most intriguingly, life span regulation. The founding member of the sirtuin family, yeast Sir2, is required for the transcriptional repression of the silent mating-type loci by altering chromatin structure through deacetylation of histones. Chromatin modification by Sir2 in yeast also underlies suppression of intrachromosomal recombination within the ribosomal RNA gene tandem repeats. Such recombination leads to an accumulation of rDNA repeats in the form of extrachromosomal circles, which are self-replicating and are preferentially retained in the mother cells, eventually causing aging by limiting yeast replicative life span. An increasing dose of Sir2 extends yeast replicative life span, whereas its loss reduces natural longevity. Although this mechanism may not be a major cause of aging in higher organisms, overexpression of Sir2 orthologs in nematodes and flies also extends life span. Sirtuins seem to specifically modulate activities that contribute to survival, probably through their mode of action, which does not simply involve hydrolyzing acetyl-lysine residues, but rather couples deacetylation to NAD hydrolysis. This mechanism offers a potential connection to the prolongevity effect—across a wide range of species—of caloric restriction (CR), which also reduces age-related diseases in rats and mice. Although the exact mechanistic basis for this relationship is controversial, CR may increase the NAD/NADH ratio, which in turn would then increase the activity of Sir2 orthologs in these different species. Indeed, increased activity of SIRT1, the Sir2 ortholog in mice, elicits a CR-like pattern of physiological changes generally associated with a longer and healthier life (Chen and Guarente, 2007). In this issue, Oberdoerffer et al. (2008) bring us back to the original findings in yeast showing that in mouse embryonic stem (ES) cells SIRT1 moves from repeat sequences and gene promoters to sites of DNA double-strand breaks (DSBs) promoting DNA repair and hence genomic stability.

The authors first demonstrate that in response to hydrogen peroxide (H_2O_2), an inducer of DNA damage that leads to chromosomal aberrations (clastogen), mating type loci in yeast are derepressed, an effect that was greatly reduced in the presence of an additional copy of Sir2. They then tested whether similar genotoxic stress-induced derepression could be demonstrated in cultured mouse ES cells. Using chromatin immunoprecipitation in combination with genome-wide promoter tiling arrays, the authors demonstrate that SIRT1 is normally bound to DNA and contributes to the silencing of major satellite repeats and hundreds of gene promoters. Similar to the situation in yeast, treatment of mouse ES cells with H_2O_2—or another clastogen, the alkylating agent methyl methane-sulfonate (MMS)—led to loss of SIRT1 binding and increased transcription at many of these loci, which could be counteracted by overexpression of SIRT1. Loss of SIRT1 binding at promoters inversely correlated with histone H1 acetylation on lysine 26 (H1AcK26), a measure of SIRT1 deacetylase activity. The question now was where did SIRT1 go in response to genotoxic stress?

Earlier work with yeast showed that Sir proteins can become redistributed from silent loci to sites of DNA repair. In their mouse ES cells, Oberdoerffer et al. found that randomly localized landing sites for SIRT1 appeared to be sites of DNA DSBs. To investigate what SIRT1 molecules are doing at these sites, the authors used reporter constructs to create one DNA DSB by the endonuclease I-SceI (Weinstock et al., 2006). The results indicate not only that SIRT1 binds to the DSB, but also that its absence interferes with the recruitment of RAD51 and NBS1, both critical players in DSB repair through homologous recombination. NBS1 is functionally linked to SIRT1 (Yuan and Seto, 2007), and defects in the repair of DSBs cause chromosomal aberrations. The investigators show that SIRT1 knockdown increases the number of chromosomal aberrations in mouse ES cells treated with H_2O_2. Finally, to conclusively demonstrate that SIRT1 is suppressing genome instability in vivo, Oberdoerffer et al. demonstrate that overexpression of SIRT1 in a mouse model that is hemizygous for the p53 tumor suppressor, after exposure to γ radiation, dramatically reduced the incidence of tumors. These results are in keeping with recent work showing that ectopic induction of SIRT1 in a mouse model of colon cancer decreases tumor formation (Firestein et al., 2008) and that mutations in SIRT1 cause genetic instability (Wang et al., 2008). Taken together, these data indicate that SIRT1 can act as a genome stabilizer.

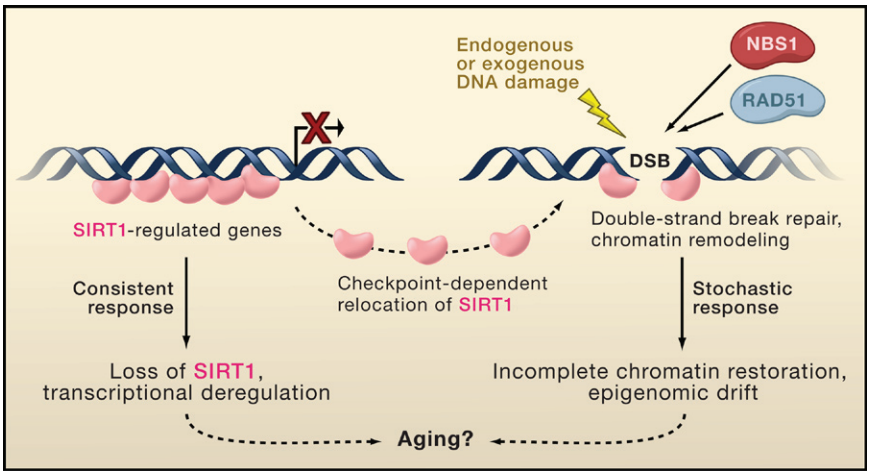

Figure 1. SIRT1, the RCM Response, and Aging

In the RCM response, SIRT1 becomes relocalized from promoters of a specific gene subset to randomly distributed DNA double-strand breaks (DSBs) induced by genotoxic stress. (Left) Although in the short term the RCM response may be transient and beneficial, chronic genotoxic stress may lead to a pattern of permanent transcriptional deregulation that is similar in most cells. (Right) This consistent response is accompanied by a stochastic response in the form of increased genomic and epigenomic errors during DNA repair under chronic genotoxic stress. Hence, aging could be a consequence of a combination of consistent and stochastic changes associated with the response to a progressively increasing frequency of damage to DNA.

Hence, both in yeast and mammalian cells, Sir2 is involved in DNA damage-induced chromatin reorganization, which Oberdoerffer et al. call an RCM or redistribution of chromatin modifiers response. These results strongly suggest that SIRT1 is involved in the kind of chromatin remodeling that we now know is an integral part of the DNA repair response (Polo and Almouzni, 2007). This confirms and extends the role of sirtuins as chromatin maintenance factors from yeast to mammals. However, the authors also link SIRT1's role in the DNA damage response to the derepression of a number of genes, many of which appear to be linked to known cellular responses to damage and which exhibit increased expression in the aged mouse brain. What is the significance of this seemingly dual mode of action of sirtuins in aging? To answer that question, we need to consider the possible long-term effects of the RCM response (Figure 1).

The repair of DNA lesions requires chromatin remodeling to mobilize repair proteins and to provide access to the lesion site (Polo and Almouzni, 2007). Some lesions such as DSBs cause rapid widespread chromatin modifications extending megabases from the break, which are mediated by ATM, H2AX, and other DNA damage response proteins, including SIRT1. Notably, Oberdoerffer et al. show that the relocalization of SIRT1 to DSBs is dependent on ATM and H2AX, which parallels the situation in yeast where the recruitment of Sir2 to DSBs requires DNA damage signaling through the ATM ortholog, MEC1. As noted by the authors, the RCM response is beneficial to the cell and the organism, with the original condition rapidly restored. However, as genotoxic stress may become chronic during aging, incomplete restoration of chromatin could be the norm, eventually challenging the integrity of the cell's genomic and epigenomic information content. Such "epigenomic drift" is essentially a stochastic process for which there is some evidence (Bahar et al., 2006). However, a chronic loss of SIRT1 from its normal regulatory targets is likely to cause a consistent pattern of gene deregulation. Indeed, whereas the new study shows mostly derepression of loci, the authors point out that loss of SIRT1 can also potentially lead to transcriptional silencing. More research is needed to uncover whether these changes have adverse effects. However, the identification of some upregulated genes that participate in cell cycle control and apoptosis suggests that a hyperactive DNA damage response may ultimately take its toll on cell and tissue homeostasis.

Oberdoerffer et al. elegantly demonstrate that some of the beneficial effects of sirtuins in mammals are surprisingly similar to those in yeast. In both cases, Sir2 and its mouse ortholog work by suppressing genome instability, which could explain the prolongevity effect of sirtuins. However, several questions remain unanswered. First, apart from SIRT1, are other chromatin modifiers involved in the RCM response, and what is their impact on aging? Second, does relocation of SIRT1 from repeat sequences increase genome instability, as it does in yeast at rDNA sites, possibly contributing to the observed increase in genome rearrangements during aging (Dollé et al., 1997)? Finally, why is the response to DNA damage so sloppy and not more carefully regulated over longer time periods? The answer to this question comes from evolutionary studies and most likely involves the steady decline in the force of natural selection with age. Given that life expectancy for mammals in the wild does not exceed the age of first reproduction by much, there is no reward in maximizing genome maintenance (Kirkwood, 2005). Be that as it may, the work of Oberdoerffer et al. is likely to stimulate further efforts to develop sirtuin-related strategies to combat aging and age-associated diseases.

REFERENCES

Bahar, R., Hartmann, C.H., Rodriguez, K.A., Denny, A.D., Busuttil, R.A., Dollé, M.E.T., Calder, R.B., Chisholm, G.B., Pollock, B.H., Klein, C.A., et al. (2006). Nature *441*, 1011–1014.

Chen, D., and Guarente, L. (2007). Trends Mol. Med. *13*, 64–71.

Dollé, M.E., Giese, H., Hopkins, C.L., Martus, H.J., Hausdorff, J.M., and Vijg, J. (1997). Nat. Genet. *17*, 431–434.

Firestein, R., Blander, G., Michan, S., Oberdoerffer, P., Ogino, S., Campbell, J., Bhimavarapu, A., Luikenhuis, S., de Cabo, R., Fuchs, C., et al. (2008). PLoS ONE *3*, e2020.

Kirkwood, T.B. (2005). Cell *120*, 437–447.

Oberdoerffer, P., Michan, S., McVay, M., Mostoslavsky, R., Vann, J., Park, S.-K., Hartlerode, A., Stegmuller, J., Hafner, A., Loerch, P., et al. (2008) Cell, this issue.

Polo, S.E., and Almouzni, G. (2007). Cell Cycle *6*, 2355–2359.

Wang, R.H., Sengupta, K., Li, C., Kim, H.S., Cao, L., Xiao, C., Kim, S., Xu, X., Zheng, Y., Chilton, B., et al. (2008). Cancer Cell *14*, 312–323.

Weinstock, D.M., Nakanishi, K., Helgadottir, H.R., and Jasin, M. (2006). Methods Enzymol. *409*, 524–540.

Yuan, Z., and Seto, E. (2007). Cell Cycle *6*, 2869–2871.